UNITED STATES DISTRICT COURT
DISTRICT OF CONNECTICUT

COLLABORATION FOR RESEARCH INTEGRITY AND TRANSPARENCY, Plaintiff, v. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, NATIONAL INSTITUTES OF HEALTH, and FOOD AND DRUG ADMINISTRATION Defendants.	Civil Action No. 3:18-cv-1181 ECF Case **[CORRECTED] COMPLAINT** July 19, 2018

INTRODUCTION

Plaintiff, Collaboration for Research Integrity and Transparency ("CRIT"), by its undersigned attorneys, alleges:

1. This action under the Administrative Procedure Act challenges an agency rule that purports to relieve medical researchers of their express statutory obligation to report basic results information for certain clinical trials involving human subjects. It further seeks to compel the defendant agencies to post public notices that are mandated by law but that they have unlawfully withheld or unreasonably delayed.

2. Clinical trial data regarding medications, medical devices, and medical treatments provide a crucial resource for clinicians, patients, researchers, policymakers, and the general public. Comprehensive reporting of this data serves to promote the integrity of clinical research, improves the quality of decisions made by clinicians and policymakers, reduces bias in scientific literature, and informs patients, clinicians, and regulators about intervention safety and effectiveness.

3. In recognition of the importance of public access to clinical trial data, Congress in 2007 required researchers conducting certain trials for approved drugs or devices to report to defendants the results of their trials. If the drugs or devices being studied were not approved at the time of a trial's completion, but were subsequently approved, Congress required the basic results information to be reported no more than 30 days after approval.

4. Congress further required defendants to make the information reported to them available to the public by means of a registry and results data bank accessible through the internet. To comply with that statutory obligation, defendants created and maintain the public website ClinicalTrials.gov.

5. Congress simultaneously required defendants to make specific, statutorily prescribed public notices on ClinicalTrials.gov whenever a researcher (1) fails to submit required clinical trial information, (2) submits false or misleading information, and/or (3) fails to submit primary or secondary outcome data, the main categories of data on which a trial focuses. Congress also required defendants to disclose the penalties they impose for any violations of the reporting requirements and to disclose whether the responsible party corrected the violation. To ensure public access to these mandatory compliance notices, Congress required defendants to provide a mechanism by which the public could easily search Clinicaltrials.gov for non-compliance notices.

6. In September 2016, or nine years after Congress imposed these requirements, defendants promulgated a final rule that contravenes the clear statutory disclosure mandates and purports to relieve parties responsible for clinical trials completed before January 18, 2017, from disclosing the basic trial results for studies of drugs or devices that were unapproved as of the trial's primary completion date, but which were subsequently approved.

7. There has been, and continues to be, widespread and well-documented failure by responsible parties to comply with their statutory reporting obligations over the last eleven years. Defendants have nevertheless failed to post even a single, statutorily required notice of non-compliance on ClinicalTrials.gov, and have failed to create a mechanism by which the public can search for instances of non-compliance.

8. Defendants' failure to enforce the statutory public disclosure mandate and to issue notices of noncompliance deprives CRIT researchers, as well as others, of the data necessary to ensure transparency in research, promote better decision-making by clinicians and policymakers, eliminate bias in the medical literature, and inform patients, clinicians, and regulators about medical product safety and effectiveness.

9. By this action, plaintiff seeks an order (a) striking down those portions of defendants' final rule purporting to relieve responsible parties of their statutory obligation to report basic results for pre-final rule clinical trials for unapproved drugs or devices that were subsequently approved; and (b) compelling defendants to issue compliance notices for any clinical trial where the responsible party has failed to satisfy its statutory reporting obligations and to make those notices easily searchable on ClinicalTrials.gov.

PARTIES

10. Plaintiff CRIT is an inter-disciplinary initiative of the Yale Law School, Yale School of Public Health, and the Yale School of Medicine launched in 2016 to enhance the quality and transparency of the research base for medical products. CRIT is jointly led by the Yale Global Health Justice Partnership, the Media Freedom & Information Access Clinic at Yale Law School, and the Yale Open Data Access ("YODA") Project within the Center for Outcomes

Research and Evaluation ("CORE") at Yale-New Haven Hospital, and the Yale School of Medicine.

11. CRIT's researchers include Dr. Joseph S. Ross, Co-Director of CRIT, Associate Professor of Medicine, and Associate Professor of Public Health, who relies upon clinical trial information to study issues related to pharmaceutical and medical device regulation, evidence development, post-market analysis of drug and device safety, and clinical adoption of drugs and devices.

12. Defendant Department of Health and Human Services ("HHS") is an agency established within the executive branch of the U.S. government and is an agency within the meaning of 5 U.S.C. § 551(1).

13. Defendant National Institutes of Health ("NIH") is an agency established within the executive branch of the U.S. government and is an agency within the meaning of 5 U.S.C. § 551(1).

14. Defendant Food and Drug Administration ("FDA") is an agency established within the executive branch of the U.S. government and is an agency within the meaning of 5 U.S.C. § 551(1).

JURISDICTION AND VENUE

15. This Court has jurisdiction pursuant to 28 U.S.C. § 1331.

16. Venue is proper under 28 U.S.C § 1391(e)(1) because plaintiff resides in this district and no real property is involved in the action.

FACTUAL ALLEGATIONS

A. Importance of Public Access to Clinical Trial Information

17. Public registration and reporting of clinical trial information provides significant benefits to researchers, regulators, policymakers, and the public at large.

18. Access to clinical trial data promotes good research practices; avoids unnecessary duplication of research; improves the credibility of research results by allowing independent scrutiny; and, enables new knowledge to be generated from meta-analyses or systematic reviews of data. Collaboration for Research Integrity and Transparency. *Promoting Transparency in Clinical Research: Why and How* 8–11 (2017), https://law.yale.edu/system/files/area/center/crit/crit_white_paper_november_2017_best_promoting_transparency_in_clinical_research_why_and_how.pdf.

19. Registration and reporting of clinical trial data must also be comprehensive to avoid biasing systematic reviews and meta-analyses, which are widely used to inform the standard of clinical care. *Id.* at 14. Such systematic reviews and meta-analyses are also important to improving medical care for subpopulations. *Id.* at 14–15.

20. Registration and reporting of clinical trial data helps clinicians, patients, and those who pay for medical treatments to accurately assess the value of medicines and make informed treatment decisions. *Id.* at 16–17.

21. Defendants NIH and HHS have both acknowledged these benefits, writing: "access to more complete information about clinical trials has both scientific and other public health benefits. The scientific benefits relate to the prevention of incomplete and biased reporting of individual trials, and the provision of information about a more complete and unbiased set of trials; the resulting set of data about clinical trials can form a more robust basis

for current medical decision making and future research planning. In addition, *ClinicalTrials.gov* provides an overview of the clinical trials enterprise, facilitating quality improvement in study focus, design, and reporting." Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64,985 (September 21, 2016).

22. Recently, Dr. Rebecca Williams, then Assistant Director of ClinicalTrials.gov, now Director, underscored that public reporting of clinical trial data "increase[s] trust in [the] clinical research enterprise." Melissa Fassbender, *NIH: 'If we don't report our results we will repeat mistakes,'* Outsourcing-Pharma.com (May 16, 2018), https://www.outsourcing-pharma.com/Article/2018/05/16/NIH-discusses-the-public-benefits-of-access-to-clinical-trial-information.

23. Dr. Jodi Black, Deputy Director of the Office of Extramural Research at NIH, has also stressed the importance of agency action to spur the public reporting of clinical trial data, saying, "sharing results should not be optional." *Id.*

24. Clinical trial data can be invaluable for researchers looking to continue the work and research of others, as well as doctors, patients, and families of patients who are seeking the most reliable treatments.

B. Congress Mandates Public Access to Clinical Trial Information

25. In 1997, Congress enacted the Food and Drug Administration Modernization Act ("FDMA"), Pub. L. No. 105-155, 111 Stat. 2296. That Act requires the Secretary of HHS, acting through the Director of NIH, to create a data bank of information on clinical trials related to drugs for serious or life-threatening diseases and to disseminate the data bank to a wide audience. FDMA § 113, 111 Stat. at 2310–12 (codified at 42 U.S.C. § 282(i)).

26. Defendant NIH subsequently created ClinicalTrials.gov to comply with defendants' obligation under the FDMA to disseminate clinical trial information, and the website was made available to the public on February 29, 2000.

27. In 2007, Congress enacted the Food and Drug Administration Amendments Act, Pub. L. No. 110–85, 121 Stat. 823 ("FDAAA"). That Act requires the Secretary of HHS, acting through the Director of NIH, to expand the clinical trials data bank "[t]o enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials," 42 U.S.C. § 282(j)(2)(A)(i).

28. Under FDAAA, "responsible parties" for "applicable clinical trials" must register those trials with the Director of NIH, and, for many applicable clinical trials, report results information. 42 U.S.C. § 282(j)(2)(A), (C); *id.* § 282(j)(3); *see* 42 C.F.R. § 11.42.

FDAAA's Registration Requirements

29. In general, FDAAA requires responsible parties to register all applicable clinical trials with the Director of NIH and submit "descriptive information," "recruitment information," "location and contact information," and "administrative data" no later than twenty-one days after the first patient is enrolled. 42 U.S.C. § 282(j)(2)(A)(ii), (C).

30. FDAAA defines "responsible party" as the sponsor of a trial, meaning the person or party who initiates the trial. 42 U.S.C. § 282(j)(1)(A)(ix). The sponsor can designate a qualified principal investigator to be the responsible party, *id.* § 282(j)(1)(A)(ix)(II), but for each trial, there may be only one responsible party, 42 C.F.R. § 11.4(c).

31. FDAAA defines "applicable clinical trials," as trials that (1) were initiated on or after September 27, 2007, or that were ongoing as of December 26, 2007, and (2) meet the following criteria set forth in 42 U.S.C. § 282(j)(1)(A)(ii)-(iii):

a. "a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes)";

b. "a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act"; or

c. "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act."

FDAAA's Results Reporting Requirements

32. Responsible parties must also submit results data for many applicable clinical trials. *See* 42 U.S.C. § 282(j)(3).

33. FDAAA mandates the submission of "[b]asic [r]esults" information for applicable clinical trials for FDA-regulated drugs and devices—*i.e.* "for each applicable clinical trial for a drug that is approved under section 355 of Title 21 or licensed under section 262 of . . . [T]itle [42] or a device that is cleared under section 360(k) of Title 21 or approved under section 360e or 360j(m) of Title 21." 42 U.S.C. § 282(j)(3)(C).

34. "Basic results" information consists of (1) demographic and baseline characteristics of patient samples; (2) primary and secondary outcomes; (3) a point of contact; and (4) whether there exists an agreement restricting the principal investigator from discussing or publishing the results of a trial. 42 U.S.C. § 282(j)(3)(C).

35. Congress required the Secretary of HHS to further expand the results reporting requirements within three years of FDAAA's enactment by issuing regulations (1) establishing whether responsible parties for clinical trials for *unapproved* devices and drugs must also submit basic results information, 42 U.S.C. § 282(j)(3)(D)(ii)(II); and (2) requiring, in addition to basic

results information, the submission of: (a) "[a] summary of the clinical trial and its results that is written in non-technical, understandable language for patients, if the Secretary determines that such types of summary can be included without being misleading or promotional"; (b) "[a] summary of the clinical trial and its results that is technical in nature, if the Secretary determines that such types of summary can be included without being misleading or promotional"; (c) "[t]he full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial"; and (d) "[s]uch other categories [of information] as the Secretary determines appropriate." 42 U.S.C. § 282(j)(3)(D)(i)–(iii) (emphasis added).

36. In general, FDAAA requires responsible parties to submit results information to the Director of NIH not later than 1 year after the earlier of (1) the estimated completion date of the trial or (2) the actual date of completion. 42 U.S.C. § 282(j)(3)(D)(iv), (E)(i). FDAAA also provides for "delayed submission" of results information for certain applicable clinical trials and for "extensions" under certain circumstances. 42 U.S.C. § 282(j)(3)(E)(iii)–(vi).

FDAAA's Results Reporting Requirements for Trials for Drugs or Devices Approved After a Trial's Completion Date

37. Congress explicitly addressed responsible parties' results reporting obligations for clinical trials for drugs or devices approved after a trial's completion date.

38. FDAAA provides:

> With respect to an applicable clinical trial that is completed before the drug is initially approved under section 355 of Title 21 or initially licensed under section 262 of this title, or the device is initially cleared under section 360(k) of Title 21 or initially approved under section 360e or 360j(m) of Title 21, the responsible party shall submit to the Director of NIH for inclusion in the registry and results data bank the clinical trial information described in subparagraphs (C) and (D) not later than 30 days after the drug or device is approved under such section 355, licensed under such section 262, cleared under such section 360(k), or approved under such section 360e or 360j(m), as applicable.

42 U.S.C. § 282(j)(5)(E)(iv).

Defendants' Obligations Under FDAAA to Provide Public Notices of Noncompliance

39. FDAAA requires the clinical trials registry and results databank to be "made publicly available through the Internet," 42 U.S.C. § 282(j)(2)(A)(i), (3)(B)(ii), codifying NIH's pre-2007 decision to make clinical trial information available via ClinicalTrials.gov.

40. Congress required defendants to issue public notices of violations of FDAAA's results reporting requirements in the data bank entry of any clinical trial for which the responsible party fails to comply with FDAAA's results reporting requirements. These notices must state that the party is not in compliance and in what way they are not in compliance, the specific penalties imposed, and whether the responsible party has corrected the information. 42 U.S.C. § 282(j)(5)(E)(i)–(ii).

41. For failure to submit required clinical information, submission of false or misleading information, and failure to submit primary and secondary outcomes, Congress prescribed the specific language that is required to be posted on ClinicalTrials.gov:

> **(iii) Failure to submit statement**
>
> The notice under clause (i) for a violation described in clause (i)(I)(aa) shall include the following statement: "The entry for this clinical trial was not complete at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry.".
>
> **(iv) Submission of false information statement**
>
> The notice under clause (i) for a violation described in clause (i)(I)(bb) shall include the following statement: "The entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law.".
>
> **(v) Non-submission of statement**
>
> The notice under clause (ii) for a violation described in clause (ii) shall include the following statement: "The entry for this clinical trial did not contain

> information on the primary and secondary outcomes at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry.".

42 U.S.C. § 282(j)(5)(E)(iii)–(v).

42. Congress further mandated that "[t]he Director of NIH shall provide that the public may easily search the registry and results data bank for entries that include notices required under this subparagraph." 42 U.S.C. § 282(j)(5)(E)(vi).

Defendants Promulgate Final Rule Implementing FDAAA's Results Reporting Requirements

43. In September 2016, defendants NIH and HHS promulgated a final rule implementing FDAAA's registration and reporting requirements. Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64,981 (September 21, 2016) (codified at 42 C.F.R. § 11) (the "Final Rule").

44. The Final Rule took effect on January 18, 2017. *Id.*

45. Under the Final Rule, and consistent with Congress's directive in FDAAA, 42 U.S.C. § 282(j)(3)(D)(ii)(II), defendants expanded FDAAA's results reporting information to include applicable clinical trials for unapproved products that have a primary completion date on or after January 18, 2017. 42 C.F.R. § 11.42.

46. Defendants also expanded the scope of the results information that responsible parties must submit to include, for example, statistical analyses for each outcome measure and adverse event information (meaning any unfavorable medical incident a patient experienced during the course of the trial). *See* 42 C.F.R. § 11.48. The additional results information required by the FDAAA Final Rule must, in general, be submitted within 1 year after the earlier of (1) the estimated completion date of the trial or (2) the actual date of completion. 42 U.S.C. § 282(j)(3)(D)(iv), (E)(i).

47. Under the final rule, NIH must post registration and results information not later than 30 calendar days after the date of submission. 42 C.F.R. §§ 11.35, 11.52.

Defendants' Final Rule Purports to Relieve Responsible Parties for Certain Clinical Trials From Their Reporting Obligations Under FDAAA

48. In contravention of FDAAA's clear text, the Final Rule purports to relieve responsible parties for pre-final rule clinical trials for drugs or devices approved after a trial's completion date from their obligation to report basic results information.

49. The Final Rule provision laying out responsible parties' reporting obligations is codified at 42 C.F.R. § 11.42.

50. That provision specifies only that responsible parties for applicable clinical trials for which the studied product is not approved, licensed, or cleared by the FDA and for which the primary completion date is *on or after January 18, 2017*, must report basic results information. 42 C.F.R. § 11.42(b).

51. The Final Rule does not require basic results information ever to be reported for applicable clinical trials with a primary completion date *before January 18, 2017*, if the drug or device was not approved until after the primary completion date (hereinafter, "pre-Rule trials for subsequently approved products" or "PRTSAPs"). *See id.*

52. The Final Rule's preamble makes plain that the Final Rule does not require responsible parties to report basic results information for PRTSAPs:

> [W]hether results information submission is required for an applicable clinical trial of an unapproved, unlicensed, or uncleared product depends on whether the primary completion date for that trial falls before or after the effective date of the regulations. If it falls before the effective date, then no results information is required to be submitted for that applicable clinical trial, regardless of whether the product studied in that clinical trial is later approved, licensed, or cleared.

Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64,981, 65,120 (Sept. 21, 2016) (codified at 42 C.F.R. § 11.2 *et seq.*).

51. Defendants' *Frequently Asked Question* guidance on ClinicalTrials.gov likewise makes plain that the Final Rule does not require responsible parties for PRTSAPs to report basic results information:

> **Am I required to submit results information for my applicable clinical trial (ACT)?**
>
> The regulations at 42 CFR 11.42 address those applicable clinical trials for which a responsible party must submit results information.
>
> . . .
>
> - For ACTs that are required to be registered and with a Primary Completion Date before January 18, 2017:
>
> - If the ACT studies a drug, biological, or device product that is approved, licensed or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. (42 CFR 11.42(a)(1))
>
> - If the ACT studies a drug, biological, or device product that is not approved, licensed, or cleared as of the Primary Completion Date, then the responsible party is not required to submit results information. (42 CFR 11.42(b))

Frequently Asked Questions, Clinicaltrials.gov (https://www.clinicaltrials.gov/ct2/manage-recs/faq#fr_6) (last visited June 20, 2018).

53. In communications with plaintiff's staff, employees of defendant agencies have further confirmed that the Final Rule does not require responsible parties for PRTSAPs to report basic results information.

C. Widespread Noncompliance with FDAAA's Registration and Results Reporting Requirements Prior to Promulgation of the Final Rule.

54. Notwithstanding FDAAA's registration and reporting requirements, including those that took effect immediately upon the statute's enactment in 2007, there has been, and remains, widespread noncompliance by responsible parties since the statute took effect.

55. For example, between 2012 and 2014, 32.8% of applicable clinical trials were registered late, and 57% of those trials were registered more than a year late. Deborah A. Zarin et al., *Update on Trial Registration 11 Years After the ICMJE Policy Was Established*, 376 New Eng. J. Med. 383 (2017).

56. A study of trials that occurred between 2008 and 2013 found that only 13.4% of responsible parties reported their results as required by 42 U.S.C. § 402(j)(3)(C) within a year of finishing the trial. Monique Anderson et al., *Compliance with Results Reporting at ClinicalTrials.gov*, 372 New Eng. J. Med. 1031 (2015).

57. As of 2013, only 37.7% of trial results had ever been reported and posted. Hiroki Saito & Christopher Gill, *How Frequently Do the Results from Completed US Clinical Trials Enter the Public Domain? — A Statistical Analysis of the ClinicalTrials.gov Database*, 9:7 PLOS (2014), https://doi.org/10.1371/journal.pone.0101826.

58. Examples of noncompliance abound. On information and belief, results are missing from numerous pivotal trials. Pivotal trials refer to the key trials on which defendants base their regulatory decision to approve a new drug or biologic. Those trials are always completed before a drug or biologic is approved, and they are the most significant evidence of a drug's safety and efficacy. Examples of pivotal trial PRTSAPs for which results should have been reported years ago but for which no results information appears on ClinicalTrials.gov include:

a. **"Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO I)."** *See A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO I)*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01252719 (primary completion date October 2012) (last updated November 14, 2012).

b. **"Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO II)."** *See A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO II)*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01252732 (primary completion date June 2013) (last updated June 26, 2013).

c. **"Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies (RECOURSE)."** *See Randomized, Double-blind, Phase 3 Study of TAS-102 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01607957 (primary completion date January 2014) (last updated October 6, 2017).

59. Similarly, on information and belief, results information for the following applicable clinical trials in pediatric populations of approved drugs and biologics should have been submitted within a year of the trials' primary completion dates—*i.e.* years ago, but no results information appears in ClinicalTrials.gov:

a. **"Primary Prevention of Hypertension in Obese Adolescents."** *See Primary Prevention of Hypertension in Obese Adolescents*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/study/NCT00288158 (primary completion date January 2011) (last updated September 14, 2017).

b. **"Biomarkers in Autism of Aripiprazole and Risperidone Treatment (BAART)."** *See Biomarkers in Autism of Aripiprazole and Risperidone Treatment*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/study/NCT01333072 (primary completion date August 2015) (last updated March 16, 2016).

c. **"Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects."** *See A Randomized, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/study/NCT01177540 (primary completion date August 2013) (last updated October 22, 2013).

60. On information and belief, two of the pediatric trials for which results have not been reported are studies required by the FDA to be completed by the manufacturer under the Pediatric Research Equity Act, 21 U.S.C. § 355c, which requires manufacturers to conduct studies in pediatric populations for new drug and biologic applications submitted on or after September 27, 2007, regarding the safety and effectiveness of the product in pediatric populations, and appropriate dosing and administration:

a. **"Safety and Efficacy Study of Ceftaroline Versus a Comparator in Pediatric Subjects With Community Acquired Bacterial Pneumonia (CABP)."** *See A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone in Pediatric Subjects With Community-acquired Bacterial Pneumonia Requiring Hospitalization,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01530763 (primary completion date August 2014) (last updated January 13, 2015).

b. **"Safety and Efficacy Study of Ceftaroline Versus a Comparator in Pediatric Subjects With Complicated Skin Infections."** *See A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01400867 (primary completion date May 2014) (last updated January 13, 2015).

61. On information and belief, other examples of trials in pediatric populations for which results information is long overdue include the sixteen trials identified in Exhibit A.

62. Noncompliance is not limited to pivotal and pediatric trials. On information and belief, results information for the following applicable clinical trials should have been reported within a year of the studies' primary completion date—*i.e.* years ago—but no results information has ever been posted on ClinicalTrials.gov:

a. "**CRLX101 in Combination With Bevacizumab for Metastatic Renal Cell Carcinoma (mRCC) Versus Standard of Care (SOC).**" *See A Randomized, Phase 2 Study to Assess the Safety and Efficacy of CRLX101 in Combination With Bevacizumab in Patients With Metastatic Renal Cell Carcinoma (RCC) Versus Standard of Care (SOC) (Investigator's Choice),* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02187302 (primary completion date July 2016) (last updated April 20, 2017).

b. **"To Determine The Efficacy and Safety of GDC-0449 in Patients With Basal Cell Nevus Syndrome (BCNS) (GDC-0449)."** *See A Randomized, Phase II Multicenter Trial Evaluating the Efficacy and Safety of a Systemic Hedgehog Pathway Antagonist (GDC-0449) in Patients With Basal Cell Nevus Syndrome (BCNS),* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT00957229 (primary completion date January 2014) (last updated June 6, 2016).

c. **"Trial Comparing the Effects of Intermittent Vismodegib vs. PDT in Patients With Multiple Basal Cell Carcinomas."** *See A Phase II Randomized, Open Label Trial Comparing the Effects of Intermittent Vismodegib Versus PDT on the Maintenance of Benefit Following 7 Months of Continuous Vismodegib Treatment in Patients With Multiple Basal Cell Carcinomas,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01556009 (primary completion date December 2015) (last updated January 14, 2016).

d. **"Apixaban Versus Warfarin in the Evaluation of Progression of Atherosclerotic Calcification and Vulnerable Plaque."** *See Apixaban Versus Warfarin in the Evaluation of Progression of Atherosclerotic Calcification and Vulnerable Plaque,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02090075 (primary completion date December 2016) (last updated May 1, 2017).

63. On information and belief, other trials for drugs or biologics approved between 2012 and 2015 for which results information is long overdue include the ten trials identified in Exhibit B.

D. Widespread Noncompliance with FDAAA's Registration and Results Reporting Requirements After Promulgation of the Final Rule.

64. Many responsible parties continue to miss their reporting deadlines even after the Final Rule, which expanded responsible parties' reporting obligations.

65. AllTrials, in conjunction with the Evidence-Based Medicine DataLab at the University of Oxford, has begun publicly documenting noncompliance with FDAAA. FDAAA Trials Tracker, http://fdaaa.trialstracker.net/ (last visited Apr. 18, 2018).

66. According to AllTrials, "major trial sponsors completed 25,927 eligible trials and ha[d not] published results for 11,714 of them" between January 2006 and November 2016. *Launch of New TrialsTracker*, AllTrials (Nov. 3, 2016), http://www.alltrials.net/news/trialstracker/. That amounts to 45.2% of trials. *Id.*

67. Additionally, AllTrials reports that only 62.4% of applicable clinical trials with completion dates *on or after* the FDAAA Final Rule effective date, January 18, 2017, have publicly reported results on ClinicalTrials.gov. FDAAA Trials Tracker, http://fdaaa.trialstracker.net/ (last visited June 19, 2018). Notably, this number only includes trials that were initially registered on ClinicalTrials.gov. *Id.* If trials that were never registered in the first place were included, the share of clinical trials for which reported information is available would be even smaller.

68. Plaintiff has identified examples of noncompliant trials that should have reported results information under the FDAAA Final Rule in Exhibit C.

E. Defendants' Knowledge or Constructive Knowledge of Noncompliance

69. Defendants collectively have the ability to identify many, if not all, applicable clinical trials for which results reporting was required under FDAAA before and after the effective date of the FDAAA Final Rule.

70. Congress itself defined "applicable clinical drugs trials" and "applicable clinical device trials" in FDAAA and specified that those applicable clinical trials for approved drugs or devices must submit results to ClinicalTrials.gov. 42 U.S.C. § 282(j)(1)(A)(i)–(iii), (3)(C).

71. FDAAA requires applications or submissions to defendant FDA for drug and device approvals to certify whether "all applicable requirements of this subsection [42 U.S.C. § 282(j)] have been met." 42 U.S.C. § 282(j)(5)(B).

72. On January 21, 2009, defendant FDA issued final guidance and a certification form (FDA 3674) implementing the statutory requirement. Final Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff: Certifications to Accompany Drug, Biologic Product, and Device Applications/Submissions, 74 Fed. Reg. 3,615 (Jan. 21, 2009). Sponsors of clinical trials must submit this certification form to FDA alongside various applications or submissions that are themselves mandatory, such as an application for a new drug approval. A true and correct copy of Certification Form FDA 3674 (revision Nov. 2008) is attached as Exhibit D.

73. Defendant FDA thus had knowledge even before the FDAAA Final Rule was issued that clinical trials referenced in applications or submissions where the sponsor certified the FDAAA requirements applied were applicable clinical trials.

74. Defendants could also have determined before the FDAAA Final Rule took effect whether other trials not identified by sponsors as covered by the reporting requirements were, in fact, covered. Non-governmental researchers were able to determine whether pre-FDAAA Final Rule trials were applicable clinical trials using only publicly available data. *See, e.g.*, Monique L. Anderson et al., *Compliance with Results Reporting at ClinicalTrials.gov*, 372 New England J. Medicine 1031 (2015); Andrew P. Prayle et al., *Compliance with Mandatory Reporting of*

Clinical Trial Results on ClinicalTrials.gov: Cross Sectional Study, 2012 BMJ 344. Given defendants' access to non-public data, they could have identified applicable clinical trials even in cases where the non-governmental researchers' analyses may have misclassified a particular clinical trial.

75. Following promulgation of the FDAAA Final Rule, defendants have knowledge of whether a trial qualifies as an applicable clinical trial that is subject to compliance with FDAAA's results reporting requirements. The Final Rule further specifies what constitutes an "applicable clinical trial" and defines with particularity what information must be submitted. *See* 42 C.F.R. § 11.22 (defining "applicable clinical trial"); *id.* § 11.28 (specifying information that must be submitted for clinical trial registration). Since promulgating the FDAAA Final Rule, defendant NIH has updated the data submission fields for ClinicalTrials.gov so that it can easily identify applicable clinical trials.

F. Defendants' Failure to Issue Public Notices of Noncompliance and Provide for Easy Searching of Those Notices

76. Notwithstanding the widespread, ongoing noncompliance with FDAAA's registration and reporting requirements, defendants, on information and belief, have never posted a public notice of noncompliance on ClinicalTrials.gov, as required by 42 U.S.C. § 282(j)(5)(E)(i)-(v).

77. There are currently no public notices on ClinicalTrials.gov for any of the clinical trials that are not in compliance with the reporting requirements of FDAAA, as required by 42 U.S.C. § 282(j)(5)(E)(i)-(v).

78. Searching the ClinicalTrials.gov database for the language of the required notices of noncompliance specified in 42 U.S.C. § 282(j)(5)(E)(i)-(v) returns no results. Exhibits E-G.

79. Site-specific searches limited to ClinicalTrials.gov on Google.com for the language of the required notices of noncompliance specified in 42 U.S.C. § 282(j)(5)(E)(iii)-(v) similarly show that no notices are posted on ClinicalTrials.gov. Exhibits H-J.

80. An inspection of the ClinicalTrials.gov entries for the clinical trials identified in paragraphs 58, 59, and 62 above that have failed to submit results information reveals no public notices of noncompliance. *See supra* ¶¶ 58, 59, 62 and accompanying citations.

81. The ClinicalTrials.gov Advanced Search feature does not contain a search field allowing the public to search the database for entries including the public notices required by 42 U.S.C. § 282(j)(5)(E)(vi). Exhibit K; *ClinicalTrials.gov Advanced Search*, https://clinicaltrials.gov/ct2/search/advanced (last visited June 19, 2018).

G. Defendants' Final Rule Purporting to Relieve Responsible Parties for PRTSAPs From Their Obligation to Report Basic Results Information and Failure to Issue Required Public Notices and Provide for Easy Searching of Those Notices Denies Researchers and Patients Access to Critical Information

82. As noted above, Congress expanded the public registry and results databank in FDAAA "[t]o enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials," 42 U.S.C. § 282(j)(2)(A)(i), and "[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials," *id.* § 282(j)(3)(D)(i).

83. On ClinicalTrials.gov itself, defendant agencies have made clear that FDAAA's registration and reporting requirements are intended to serve the general public, patients, the research community, clinicians, users of medical literature, journal editors, agencies providing grant funding for clinical trials, the research community, institutional review boards,[1] ethicists,

[1] Institutional review boards (IRBs) ensure that research methods, including clinical trials, comply with appropriate ethical requirements. To be effective, IRBs need to evaluate whether a research protocol is appropriate; full registration and reporting of results on ClinicalTrials.gov can aid that evaluation.

and policy makers. *Why Should I Register and Submit Results?*, ClinicalTrials.gov (page last reviewed March 2018), https://clinicaltrials.gov/ct2/managerecs/background#WhatIsThePurpose.

84. Plaintiff CRIT is entitled to the results information for PRTSAPs, 42 U.S.C. § 282(j)(5)(E)(iv); notices of noncompliance, 42 U.S.C. § 282(j)(5)(E)(i)-(v); and access to a mechanism to "easily search the registry and results data bank for entries that include notices" of noncompliance, 42 U.S.C. § 282(j)(5)(E)(vi).

85. Defendant agencies' failure to requires responsible parties for PRTSAPs to report basic results information, *see* 42 C.F.R. § 11.42, denies CRIT information to which it is entitled by law.

86. Defendant agencies' failure to make available the notices required by 42 U.S.C. § 282(j)(5)(E) denies CRIT information to which it is entitled by law.

87. Defendant agencies' failure to make available a public search function required by 42 U.S.C. § 282(j)(5)(E) denies CRIT information to which it is entitled by law by preventing plaintiff from searching for notices of non-compliance, particularly with respect to statutorily required notices of noncompliance for which FDAAA does not mandate specific language.[2]

88. Together, these actions deprive CRIT researchers, as well as others, of the data necessary to ensure transparency in research, promote better decision-making by clinicians and policymakers, eliminate bias in the medical literature, and to make patients, clinicians, and regulators aware of medical product safety and effectiveness.

89. Among other issues, CRIT's researchers study the integrity of the clinical trial research enterprise and issues related to pharmaceutical and medical device regulation, evidence

[2] For example, NIH must post notices detailing any penalties imposed and whether the responsible party has corrected the information in ClinicalTrials.gov, but FDAAA does not mandate any specific language for these notices. 42 U.S.C. § 282(j)(5)(E)(i)(II)–(III).

development and dissemination, post-market surveillance, and clinical adoption and publish papers on said topics.

90. Plaintiff CRIT and its researchers have spent and will continue to spend time attempting to identify trials that are out of compliance, the reason why those trials are out of compliance, whether defendant agencies have taken any action to correct the noncompliance, and whether the responsible party has corrected the information.

91. Without the basic results information for PRTSAPs, CRIT's researchers are unable to characterize the integrity of the clinical trial research enterprise and issues related to pharmaceutical and medical device evidence development and dissemination.

92. Without the statutorily required notices and search function, CRIT's researchers must expend substantial time and resources to attempt to identify noncompliant trials. First, they must conduct a series of advanced searches on ClinicalTrials.gov to identify potentially applicable clinical trials for which results are not reported by, for example, filtering trials by completion date, interventional status, the location of the study, and other relevant variables. Then, CRIT's researchers must analyze each potentially applicable clinical trial one-by-one to determine the probability that the trial is not in compliance by analyzing, among other things, whether the responsible party was granted an extension or submitted results which are not yet posted.

93. Ultimately, without the statutorily required notices, CRIT's researchers are unable to rely on the accuracy of their assessments about trials' compliance with FDAAA's reporting requirements or fully characterize the integrity of the clinical trial research enterprise and issues related to pharmaceutical and medical device evidence development and dissemination.

FIRST CLAIM
Violation of APA—Unlawful Statutory Interpretation

94. Plaintiff repeats, realleges, and incorporates the allegations in the foregoing paragraphs as though fully set forth herein.

95. The APA, 5 U.S.C. § 706(2)(A), (C), provides that a reviewing court shall hold unlawful and set aside agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," and that is "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right."

96. In purporting to relieve certain responsible parties of their statutory obligation under 28 U.S.C. § 282(j)(5)(E)(iv) to report basic clinical trial results for PRTSAPs, the Final Rule is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and is in excess of defendants' statutory jurisdiction, authority, or limitations, within the meaning of 5 U.S.C. § 706(2)(A) and (C).

97. CRIT and its researchers are directly aggrieved by defendants' final agency action.

SECOND CLAIM
Violation of APA – Agency Action Unlawfully Withheld and/or Unreasonably Delayed

98. Plaintiff repeats, realleges, and incorporates the allegations in the foregoing paragraphs as though fully set forth herein.

99. Defendants have a non-discretionary obligation under 42 U.S.C. § 282(j)(5)(E)(i)-(v) to issue and post public notices of noncompliance for applicable clinical trials that do not register and report as required by FDAAA and the FDAAA Final Rule.

100. Defendants have a non-discretionary obligation under 42 U.S.C. § 282(j)(5)(E)(vi) to create a public search function for notices of noncompliance on ClinicalTrials.gov.

101. Defendants' failure to issue and post public notices of noncompliance for clinical trials, and their failure to create a search function for notices of noncompliance on ClinicalTrials.gov, constitutes agency action unlawfully withheld and/or unreasonably delayed, in violation of 5 U.S.C. § 706(1).

102. Defendants are on notice that responsible parties for certain applicable clinical trials which initiated on or after January 18, 2017, should have reported, but have not reported, results information for those trials.

103. Defendants have issued no notices of noncompliance, agency enforcement action, or whether responsible parties have corrected the results reporting deficiency.

104. CRIT is injured by defendants' failure to post notices of penalties imposed for responsible parties' failure to comply with FDAAA's reporting requirements mandated by 42 U.S.C. § 282(j)(5)(E)(i)(II). Without these notices, CRIT's researchers are unable to ascertain whether a responsible party has properly registered said clinical trial and reported results as required by law; analyze that information to inform CRIT's efforts to characterize the integrity of the clinical research enterprise; and make patients, clinicians, and regulators aware of all research that offers insight into medical product safety and effectiveness.

105. CRIT is injured by defendants' failure to post notices indicating whether a responsible party has corrected any error in its reporting of clinical trial information required by 42 U.S.C. § 282(j)(5)(E)(i)(III). Without these notices, CRIT's researchers are unable to rely on this information in their efforts to characterize the integrity of the clinical research enterprise, and to make patients, clinicians, and regulators aware of all research that offers insight into medical product safety and effectiveness.

106. CRIT is injured by defendants' failure to post failure-to-submit notices required by 42 U.S.C. § 282(j)(5)(E)(iii). Without these notices, CRIT's researchers are unable to ascertain whether a responsible party has properly reported clinical trial results as required by law; analyze this information in their efforts to characterize the integrity of the clinical research enterprise; and make patients, clinicians, and regulators aware of all research that offers insight into medical product safety and effectiveness.

107. CRIT is injured by defendants' failure to post submission-of-false-information notices required by 42 U.S.C. § 282(j)(5)(E)(iv). Without these notices, CRIT's researchers are unable to rely on the accuracy of clinical trial information in their efforts to characterize the integrity of the clinical research enterprise, and to make patients, clinicians, and regulators aware of all research that offers insight into medical product safety and effectiveness.

108. CRIT is injured by defendants' failure to post non-submission-of-primary-and-secondary-outcomes notices required by 42 U.S.C. § 282(j)(5)(E)(ii), (v). Without these notices, CRIT's researchers are unable to ascertain whether a responsible party has properly reported results as required by law; analyze that information to inform CRIT's efforts to characterize the integrity of the clinical research enterprise; and make patients, clinicians, and regulators aware of all research that offers insight into medical product safety and effectiveness.

109. CRIT is injured by defendants' failure to provide a search field for notices of non-compliance required by 42 U.S.C. § 282(j)(5)(E). Without this search capability, CRIT's researchers are unable to ascertain whether a responsible party has properly registered its clinical trial and reported results as required by law; analyze that information to inform CRIT's efforts to characterize the integrity of the clinical research enterprise; and make patients, clinicians, and regulators aware of all research that offers insight into medical product safety and effectiveness.

110. As a result, CRIT, including its researchers, are unable to track the progress of clinical trials, the overall compliance rates with FDAAA's reporting requirements, and defendants' enforcement efforts, or to convey that information to the broader public.

111. Instead, to ascertain even some of the information that would otherwise be provided by FDAAA's required notices, CRIT must expend time and resources attempting to compile the information through other, significantly less efficient means. Even then, CRIT cannot fully reverse engineer the information that would be provided by FDAAA's statutory notices.

THIRD CLAIM
Violation of APA – Agency Action Contrary To Law

112. Plaintiff repeats, realleges, and incorporates the allegations in the foregoing paragraphs as though fully set forth herein.

113. Defendants' failure to comply with the Public Health Service Act, 42 U.S.C. § 282(j)(5)(E)—*i.e.*, their failure to issue and post public notices of noncompliance for applicable clinical trials that do not register and report, and to create a search field for such notices, as required by FDAAA and the FDAAA Final Rule—is agency action contrary to law in violation of the Administrative Procedure Act, 5 U.S.C. § 706(2)(A)(C).

114. CRIT and its researchers are directly aggrieved by defendants' failure to create the search function required by FDAAA as it must expend time and resources searching ClinicalTrials.gov for individual notices of noncompliance.

RELIEF REQUESTED

WHEREFORE, plaintiff respectfully requests this Court to:

A. Declare that defendants' Final Rule violates the Public Health Service Act by purporting to relieve responsible parties for PRTSAPs of their statutory obligation under 28 U.S.C. § 282(j)(5)(E)(iv) to report basic results.

B. Enjoin defendants to enforce the mandatory obligation to report basic clinical trial results set forth in28 U.S.C. § 282(j)(5)(E)(iv) for PRTSAPs.

C. Declare that defendants' failure to issue and post on ClinicalTrials.gov public notices of noncompliance for applicable clinical trials that do not register and report as required FDAAA and the FDAAA Final Rule are agency action contrary to law, unlawfully withheld, and unreasonably delayed;

D. Enjoin defendants to comply with the substantive provisions of FDAAA and the FDAAA Final Rule that require them to issue and post public notices of noncompliance on ClinicalTrials.gov;

E. Enjoin defendants to comply with the substantive requirements of FDAAA by creating a search function for notices of noncompliance on ClinicalTrials.gov;

F. Award plaintiff its costs and reasonable attorneys' fees under 28 U.S.C. § 2412; and

G. Grant such other and further relief as the Court deems just and proper.

Dated: July 19, 2018

Respectfully submitted,

MEDIA FREEDOM & INFORMATION ACCESS CLINIC

By: /s/ David Schulz

David Schulz, supervising attorney
(Bar Number CT30427)
John Langford, supervising attorney
(*pro hac vice* application forthcoming)
Christine D'Alessandro, law student intern
Isabel Farhi, law student intern
Abby McCourt, law student intern
Adam Pan, law student intern
MEDIA FREEDOM & INFORMATION
ACCESS CLINIC
ABRAMS INSTITUTE
Yale Law School
P.O. Box 208215
New Haven, CT 06520-8215
Tel: (203) 436-5831
Fax: (203) 432-3034
john.langford@yale.edu

Counsel for Plaintiff

EXHIBIT A

Pediatric Trials Without Results Reported

1. **"Primary Prevention of Hypertension in Obese Adolescents"** *See Primary Prevention of Hypertension in Obese Adolescents,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT00288158 (primary completion date January 2011) (last updated September 14, 2017).

2. **"Biomarkers in Autism of Aripiprazole and Risperidone Treatment (BAART)"** *See Biomarkers in Autism of Aripiprazole and Risperidone Treatment,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01333072 (primary completion date August 2015) (last updated March 16, 2016).

3. **Buspirone in the Treatment of 2-6 Year Old Children With Autistic Disorder (B-ACE)"** *See A Randomized, Placebo-controlled, Double-masked Clinical Trial of Buspirone in the Treatment of 2- 6 Year Old Children With Autistic Disorder,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/record/NCT00873509 (primary completion date January 2015) (last updated July 26, 2016).

4. **"Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects"** *See A Randomized, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01177540 (primary completion date January 2013) (last updated October 22, 2013).

5. **"A Study of Combination Therapy in Children With ADHD"** *See A Double-Blind Placebo-Controlled Study of Combination Therapy in Children With ADHD,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01940978 (primary completion date March 2015) (last updated April 10, 2015).

6. **"Identification and Treatment of Clinically Silent Catheter-Related Deep Vein Thrombosis in Children With Cancer"** *See Phase II Study on the Identification and Treatment of Clinically Silent Catheter-Related Deep Vein Thrombosis in Children With Cancer,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT00633061 (primary completion date December 2011) (last updated February 7, 2013).

7. **"Efficacy and Safety Study Comparing Lorazepam and Diazepam for Children in the Emergency Department With Seizures (Status 2)"** *See Use Of Lorazepam For The Treatment Of Pediatric Status Epilepticus: A Randomized, Double-Blinded Trial Of Lorazepam And Diazepam,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT00621478 (primary completion date May 2012) (last updated December 18, 2012).

8. **"A Multi-site Double-blind Placebo-controlled Trial of Memantine Versus Placebo in Children With Autism (MEM)"** *See A Multi-site Double-blind Placebo-controlled Trial of Memantine Versus Placebo in Children With Autism Targeting Memory and Motor Planning,*ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01372449 (primary completion date October 2015) (last updated March 20, 2017).

9. **"Subcutaneous Rehydration Compared to Intravenous Rehydration (PEDs-II)"** *See Subcutaneous Rehydration With Hylenex Compared to Intravenous Rehydration in Infants and Young Children With Mild to Moderate Dehydration,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT00773175 (primary completion date December 2009) (last updated December 5, 2011).

10. **"Risperidone Treatment In Children With Autism Spectrum Disorder And High Levels Of Repetitive Behavior (ProjectV)"** *See Risperidone Treatment In Children With Autism Spectrum Disorder And High Levels of Repetitive Behavior,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01171937 (primary completion date September 2016) (last updated May 3, 2017).

11. **"Study of Rufinamide in Pediatric Subjects 1 to Less Than 4 Years of Age With Lennox-Gastaut Syndrome Inadequately Controlled With Other Anti-epileptic Drugs"** *See A Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to Less Than 4 Years of Age With Inadequately Controlled Lennox-Gastaut Syndrome,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01405053 (primary completion date October 2015) (last updated March 23, 2016).

12. **"A Pilot Study to Assess the Glucose Lowering Effect of Metformin and Sitagliptin in Adolescents With Type 1 Diabetes"** *See A Pilot Study to Assess the Glucose Lowering Effect of Metformin and Sitagliptin in Adolescents With Type 1 Diabetes Mellitus,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01718093 (primary completion date December 2015) (last updated April 24, 2017).

13. **"Topiramate in Neonates Receiving Whole Body Cooling for Hypoxic Ischemic Encephalopathy"** *See Topiramate As An Adjuvant To Therapeutic Hypothermia For Infants With Hypoxic Ischemic Encephalopathy,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01765218 (primary completion date May 2016) (last updated June 12, 2018).

14. **"Safety and Efficacy of Vilazodone in Adolescent Patients With Major Depressive Disorder (VLZ-MD-21)"** *See A Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Vilazodone in Adolescent Patients With Major Depressive Disorder,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01878292 (primary completion date March 2016) (last updated October 7, 2016).

15. **"Safety and Efficacy Study of Ceftaroline Versus a Comparator in Pediatric Subjects With Community Acquired Bacterial Pneumonia (CABP)."** *See A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone in Pediatric Subjects With Community-acquired Bacterial Pneumonia Requiring Hospitalization,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01530763 (primary completion date August 2014) (last updated January 13, 2015).

16. **"Safety and Efficacy Study of Ceftaroline Versus a Comparator in Pediatric Subjects With Complicated Skin Infections."** *See A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01400867 (primary completion date May 2014) (last updated January 13, 2015).

EXHIBIT B

New Molecular Entities Approved 2012 to 2015 Without Results Reported

1. "**CRLX101 in Combination With Bevacizumab for Metastatic Renal Cell Carcinoma (mRCC) Versus Standard of Care (SOC).**" *See A Randomized, Phase 2 Study to Assess the Safety and Efficacy of CRLX101 in Combination With Bevacizumab in Patients With Metastatic Renal Cell Carcinoma (RCC) Versus Standard of Care (SOC) (Investigator's Choice),* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02187302 (primary completion date July 2016) (last updated April 20, 2017).

2. **"To Determine The Efficacy and Safety of GDC-0449 in Patients With Basal Cell Nevus Syndrome (BCNS) (GDC-0449)."** *See A Randomized, Phase II Multicenter Trial Evaluating the Efficacy and Safety of a Systemic Hedgehog Pathway Antagonist (GDC-0449) in Patients With Basal Cell Nevus Syndrome (BCNS),* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT00957229 (primary completion date January 2014) (last updated June 6, 2016).

3. **"Trial Comparing the Effects of Intermittent Vismodegib vs. PDT in Patients With Multiple Basal Cell Carcinomas."** *See A Phase II Randomized, Open Label Trial Comparing the Effects of Intermittent Vismodegib Versus PDT on the Maintenance of Benefit Following 7 Months of Continuous Vismodegib Treatment in Patients With Multiple Basal Cell Carcinomas,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01556009 (primary completion date December 2015) (last updated January 14, 2016).

4. **"A Multicenter, Double-blind, Randomized, Parallel-group, Pilot Study of 12-week Duration to Assess the Short-term Safety and Tolerability of Lorcaserin Plus Two Doses of Immediate-Release Phentermine-HCl Compared With Lorcaserin Alone in Overweight and Obese Adults"** *See A Multicenter, Double-blind, Randomized, Parallel-group, Pilot Study of 12-week Duration to Assess the Short-term Safety and Tolerability of Lorcaserin Plus Two Doses of Immediate-Release Phentermine-HCl Compared With Lorcaserin Alone in Overweight and Obese Adults,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01987427 (primary completion date August 2014) (last updated January 26, 2015).

5. **"Apixaban Versus Warfarin in the Evaluation of Progression of Atherosclerotic Calcification and Vulnerable Plaque."** *See Apixaban Versus Warfarin in the Evaluation of Progression of Atherosclerotic Calcification and Vulnerable Plaque,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02090075 (primary completion date December 2016) (last updated May 1, 2017).

6. **"A Study of the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients With Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol (FOCUS FH)"** *See, A Phase 3, Randomized, Double-*

Blind, Placebo-Controlled, Parallel-Group Study Followed by an Open-Label Continuation Period to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients With Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01475825 (primary completion date February 2016) (last updated August 3, 2016).

7. **"Sentinel Lymph Node Mapping Post-Injection Site Pain"** *See A Randomized, Double-blinded, Controlled Clinical Trial Comparing Post-injection Site Pain of Technetium-labeled Tilmanocept Versus Technetium-labeled Sulfur Colloid in Patients Undergoing Sentinel Lymph Node Mapping Procedure for Breast Cancer,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02065232 (primary completion date February 2015) (last updated July 27, 2015).

8. **"An Efficacy and Safety Study of Simeprevir and Sofosbuvir With and Without Ribavirin in Participants With Recurrent Genotype 1 Hepatitis C Post-Orthotopic Liver Transplant (GALAXY)"** *See A Phase 2 Open-Label Study in Patients With Recurrent Genotype 1 Hepatitis C Post-Orthotopic Liver Transplant to Explore the Safety And Efficacy of Simeprevir and Sofosbuvir With and Without Ribavirin,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02165189 (primary completion date November 2015) (last updated November 11, 2016).

9. **"Safety Study of ATX-101 in Subjects With Varying Chin Sizes"** *See A Multicenter, Double-blind, Placebo-controlled Safety Study of ATX-101 (Deoxycholic Acid Injection) for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects With Clinician-Reported Submental Fat Rating Scale (CR SMFRS) Grade 1 or CR-SMFRS Grade 4,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02035267 (primary completion date June 2015) (last updated August 4, 2015).

10. **"Safety Study of ATX-101 for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects 65 to 75 Years of Age"** *See A Multicenter, Double-blind, Placebo-controlled Safety Study of ATX-101 (Deoxycholic Acid Injection) for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects 65 to 75 Years of Age,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02123134 (primary completion date August 2015) (last updated September 22, 2015).

EXHIBIT C

Trials Completed after Effective Date of Final Rule without Results Reported

1. **"Mepivacaine vs. Bupivacaine Spinal Anesthetic in Total Knee Arthroplasty."** *See Mepivacaine vs. Bupivacaine Spinal Anesthetic in Total Knee Arthroplasty, a Randomized Controlled Clinical Trial,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/ NCT02980926 (primary completion date March 2017) (last updated March 27, 2017).

2. **"Intravenous Sub-dissociative Dose Ketamine Injection Versus Infusion for Analgesia in the Emergency Department."** *See Intravenous Sub-dissociative Dose Ketamine Injection Versus Infusion for Analgesia in the Emergency Department: A Prospective, Randomized, Double-blind Placebo Controlled Trial,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/ results/NCT02916927 (primary completion date April 2017) (last updated May 5, 2017).

3. **"A Treatment for Severe Inflammatory Acne Subjects."** *See Efficacy and Safety of Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel Plus Doxycycline in Severe Inflammatory Acne (Non-Nodulocystic) Subjects,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/ NCT02899000 (primary completion date March 28, 2017) (last updated November 1, 2017).

4. **"Esmolol Infusion for Patients With Septic Shock and Persistent Tachycardia."** *See Esmolol to Control Adrenergic Storm in Septic Shock - Roll-in,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02841241 (primary completion date March 2017) (last updated January 8, 2018).

5. **"A Clinical Trial to Evaluate the Efficacy of Two Acne Treatments."** *See A Multi-Center Clinical Trial to Evaluate the Efficacy of Two Acne Treatments,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02755545 (primary completion date April 4, 2017) (last updated August 2, 2017).

6. **"A Pilot Study Comparing Anti-Inflammatory Effects Of TXA Versus EACA In Pediatric Congenital Heart Surgery."** *See A Pilot Study Comparing Anti-Inflammatory Effects Of Tranexamic Acid Versus Epsilon Aminocaproic Acid In Pediatric Congenital Heart Surgery,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02656472 (primary completion date April 2017) (last updated April 20, 2017).

7. **"Bilateral Comparison of Treatment of Facial Actinic Keratoses Using Microneedling and Photodynamic Therapy With Aminolevulinic Acid and Blue Light Versus Photodynamic Therapy With Aminolevulinic Acid and Blue Light Using Two Incubation Times."** *See A Randomized, Evaluator-blinded, Bilateral Comparison of the Treatment of Facial Actinic Keratoses Using Combination Microneedling and Photodynamic Therapy With Aminolevulinic Acid and Blue Light Versus Photodynamic Therapy With Aminolevulinic Acid and Blue Light Using Two Different Incubation Times,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/

results/NCT02622594 (primary completion date April 13, 2017) (last updated July 19, 2017).

8. **"Treatment of Hemoglobin SC Disease."** *See SC Youth Treatment With Hydroxyurea Effects,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02336373 (primary completion date March 31, 2017) (last updated August 28, 2017).

9. **"Study of Lamotrigine to Treat Ménière's Disease."** *See Lamotrigine for Ménière's Disease: a Double-blind, Placebo-controlled Pilot Study,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/ show/results/NCT02158585 (primary completion date March 2017) (last updated July 28, 2017).

10. **"Efficacy of Recombinant FSH/GnRH Antagonist Protocol With and Without LH Adjunct for Egg Bank Donation."** *See Efficacy of Recombinant FSH/GnRH Antagonist Protocol With and Without LH Adjunct and GnRH Agonist Trigger for Egg Bank Donation,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02069808 (primary completion date February 12, 2017) (last updated March 23, 2018).

11. **"A Randomized Controlled Trial of Cognitive Remediation and D-cycloserine for Individuals With Bipolar Disorder."** *See* A *Randomized Controlled Trial of Cognitive Remediation and D-cycloserine for Individuals With Bipolar Disorder,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01934972 (primary completion date April 2017) (last updated April 25, 2017).

12. **"Lenalidomide and Dexamethasone With/Without Stem Cell Transplant in Patients With Multiple Myeloma."** *See A Randomized Clinical Trial of Lenalidomide (CC-5013) and Dexamethasone With and Without Autologous Peripheral Blood Stem Cell Transplant in Patients With Newly Diagnosed Multiple Myeloma,* ClinicalTrials.gov, https://clinicaltrials.gov/ ct2/show/results/NCT01731886 (primary completion date April 11, 2017) (last updated January 30, 2018).

13. **"Quetiapine Pharmacotherapy for Cannabis Dependence."** *See Quetiapine Pharmacotherapy for Cannabis Dependence,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/ NCT01697709 (primary completion date April 30, 2017) (last updated May 21, 2018).

14. **"Pilot Study of Velcade® in IgA Nephropathy."** *See Velcade Therapy for Severe IgA Nephropathy,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01103778 (primary completion date April 17, 2017) (last updated May 1, 2018).

15. **"Short-Term Oral Mifepristone for Central Serous Chorioretinopathy."** *See Short-Term Oral Mifepristone for Central Serous Chorioretinopathy. A Placebo-controlled Dose Ranging Study of Mifepristone in the Treatment of CSC (STOMP-CSC),* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02354170 (primary completion date April 27, 2017) (last updated July 26, 2017).

16. **"Safety and Tolerability Study of NBI-98854 for the Treatment of Tardive Dyskinesia."** *See A Phase 3, Open-Label, Safety and Tolerability Study of NBI-98854 for the Treatment of Tardive Dyskinesia,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT02405091 (primary completion date March 2017) (last updated March 17, 2017).

17. **"Clozapine for Cannabis Use in Schizophrenia."** *See Clozapine for Cannabis Use Disorder in Schizophrenia,* ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01639872 (primary completion date March 29, 2017) (last updated March 23, 2018).

18. **"Temsirolimus and Bevacizumab in Treating Patients With Advanced Endometrial, Ovarian, Liver, Carcinoid, or Islet Cell Cancer."** See A Phase 2 Trial of Temsirolimus and Bevacizumab in Patients With Endometrial, Ovarian, Hepatocellular Carcinoma, Carcinoid or Islet Cell Cancer, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/results/NCT01010126 (primary completion date March 13, 2017) (last updated July 11, 2017).

EXHIBIT D

See OMB Statement on Reverse. Form Approved: OMB No. 0910-0610. Expiration Date: 10-31-2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER	2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
3. ADDRESS *(Number, Street, State, and ZIP Code)*	4. TELEPHONE AND FAX NUMBERS *(Include Area Code)* (Tel.) ..... (Fax) .....

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
(Attach extra pages as necessary)

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☐ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/ SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*

NCT Number(s):

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)	12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11 (Name) ..... (Title)	
13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)*	14. TELEPHONE AND FAX NUMBERS *(Include Area Code)* (Tel.) ..... (Fax)	15. DATE OF CERTIFICATION

PSC Graphics: (301) 443-1090 EF

Instructions for Completion of Form FDA 3674

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))
Form 3674 must accompany an application/submission, including amendments, supplements, and resubmissions, submitted under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.

1. **Name of Sponsor/Applicant/Submitter -** This is the name of the sponsor/applicant/submitter of the drug/biologic/device application/ submission which the certification accompanies. The name must be identical to that listed on the application/submission.
2. **Date -** This is the date of the application/submission which the certification accompanies.
3. **& 4. -** Provide complete address, telephone number and fax number of the sponsor/applicant/submitter.
5. **Product Information - For Drugs/Biologics:** Provide the established, proprietary name, and/or chemical/biochemical/blood product/ cellular/gene therapy name(s) for the product covered by the application/submission. Include all available names by which the product is known. **For Devices:** Provide the common or usual name, classification, trade or proprietary or model name(s), and/or model number(s). Include all available names/model numbers by which the product is known.
6. **Type of Application/Submission -** Identify the type of application/submission which the certification accompanies by checking the appropriate box. If the name of the type of application/submission is not identified, check the box labeled "Other."
7. **IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/Other Number -** If FDA has previously assigned a number associated with the application/ submission which this certification accompanies, list that number in this field. For example, if the application/submission accompanied by this certification is an IND protocol amendment and the IND number has already been issued by FDA, that number should be provided in this field.
8. **Serial Number -** In some instances a sequential serial number is assigned to the application. If there is such a serial number, provide it in this field. If there is no such number, leave this field blank.
9. **Certification -** This section contains three different check-off boxes.

   Box A should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply because no clinical trials are included, relied upon, or otherwise referred to, in the application/ submission which the certification accompanies.

   Box B should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply at the time of submission of the certification to any clinical trials that are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. This means that, even though some or all of the clinical trials included, relied upon, or otherwise referred to in the application/submission may be “applicable clinical trials” under 42 U.S.C. § 282(j)(1)(A)(i), section 402(j)(1)(A)(i) of the Public Health Service Act, on the date the certification is signed, 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, does not require that any information be submitted to the ClinicalTrials.gov Data Bank with respect to those clinical trials.

   Box C should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do apply, on the date the certification is signed, to some or all of the clinical trials that are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. This means that, as of the date the certification is signed, the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies.
10. **National Clinical Trial (NCT) Numbers -** If you have checked Box C in number 9 (Certification), provide the NCT Number obtained from www.ClinicalTrials.gov for each clinical trial that is an "applicable clinical trial" under 42 U.S.C. § 282(j)(1)(A)(i), section 402(j)(1)(A)(i) of the Public Health Service Act, and that is included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. Type only the number, as the term "NCT" will be added automatically before number. Include any and all NCT numbers that, as of the date the certification is signed, have been assigned to the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies. Multiple NCT numbers may be required for a particular certification, depending on the number of "applicable clinical trials" included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. Leave this field blank if you have checked Box 9.C but, at the time the certification is completed, you have not yet received any NCT numbers for the "applicable clinical trial(s)" included, relied upon, or otherwise referred to in the application/ submission.
11. **Signature of Sponsor/Applicant/Submitter or an Authorized Representative -** The person signing the certification must sign in this field.
12. **Name and Title of Person Who Signed in number 11 -** Include the name and title of the person who is signing the certification. If the person signing the certification is not the sponsor/applicant/submitter of the application/submission, he or she must be an authorized representative of the sponsor/applicant/submitter.
13. **& 14. -** Provide the full address, telephone and fax numbers of the person who is identified in number 11 and signs the certification in number 11.
15. Provide the date the certification is signed. This date may be different from the date provided in number 2.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/submission) per response, including time for reviewing instructions. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the address below.

Department of Health and Human Services
Food and Drug Administration
Office of the Chief Information Officer (HFA-250)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information, unless it displays a currently valid OMB control number.

EXHIBIT E

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Modify Search Start Over

No Studies found for: **"The entry for this clinical trial was not complete at the time of submission, as required by law."**

Your search found no studies.

Modify your search, check for misspellings, try other words.

List | By Topic | On Map | Search Details

Hide Filters

Subscribe to RSS

Filters

Apply Clear

Recruitment Status

Clinical Study :

- [ ] Not yet recruiting
- [ ] Recruiting
- [ ] Enrolling by invitation
- [ ] Active, not recruiting
- [ ] Suspended
- [ ] Terminated
- [ ] Completed
- [ ] Withdrawn
- [ ] Unknown status†

Expanded Access :

Eligibility Criteria

Age :

[ ] years OR

Age Group:

- [ ] Child (birth–17)
- [ ] Adult (18–65)
- [ ] Senior (66+)

Sex ⓘ :

- (•) All
- ( ) Female
- ( ) Male

[ ] Accepts Healthy Volunteers ⓘ

Study Type ⊞

Study Results ⊞

Study Phase ⊞

Funder Type ⊞

Apply **Clear**

EXHIBIT F

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Hide Search Start Over

Condition or disease

x

Other terms

"The entry for this clinical trial was found to be false or misleading and therefore not in compliance wi x

Country

x

Search Advanced Search

No Studies found for: **"The entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law."**

Your search found no studies.

Modify your search, check for misspellings, try other words.

List By Topic On Map Search Details

Hide Filters Subscribe to RSS

Filters

Apply Clear

Recruitment Status

Clinical Study :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended

- [ ] Terminated
- [ ] Completed
- [ ] Withdrawn
- [ ] Unknown status†

Expanded Access :

Eligibility Criteria

Age :

years OR

Age Group:

- [ ] Child (birth–17)
- [ ] Adult (18–65)
- [ ] Senior (66+)

Sex :

- (•) All
- ( ) Female
- ( ) Male

- [ ] Accepts Healthy Volunteers

Study Type

Study Results

Study Phase

Funder Type

Apply Clear

EXHIBIT G

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Hide Search Start Over

Condition or disease

Other terms

"The entry for this clinical trial did not contain information on the primary and secondary outcomes at

Country

Search Advanced Search

No Studies found for: **"The entry for this clinical trial did not contain information on the primary and secondary outcomes at the time of submission, as required by law."**

Your search found no studies.

Modify your search, check for misspellings, try other words.

List | By Topic | On Map | Search Details

Hide Filters Subscribe to RSS

Filters

Apply Clear

Recruitment Status

Clinical Study :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended

- [ ] Terminated
- [ ] Completed
- [ ] Withdrawn
- [ ] Unknown status†

Expanded Access :

Eligibility Criteria

Age :

years OR

Age Group:

- [ ] Child (birth–17)
- [ ] Adult (18–65)
- [ ] Senior (66+)

Sex :

- ( ) All
- ( ) Female
- ( ) Male

[ ] Accepts Healthy Volunteers

Study Type

Study Results

Study Phase

Funder Type

Apply Clear

EXHIBIT H

Google site:clinicaltrials.gov "The entry for this clinical trial was not complete at t

All News Videos Images Shopping More Settings Tools

About 99,700 results (0.86 seconds)

No results found for **site:clinicaltrials.gov "The entry for this clinical trial was not complete at the time of submission, as required by law."**.

Results for **site:clinicaltrials.gov The entry for this clinical trial was not complete at the time of submission, as required by law.** (without quotes):

FDAAA 801 and the Final Rule - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/fdaaa
For **complete** Final Rule **requirements**, please refer to 42 CFR Part 11. ... for any use and that are **required** to be registered, **full** posting of the **clinical trial** information ..... is **submitted**, if neither of the events listed above has occurred by that **time**. .... History of ClinicalTrials.gov: See History, Policies, and **Laws** for information on ...
Who Is Responsible for ... · Which Trials Must Be ... · Which Trials Must Have ...

Frequently Asked Questions - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/faq
I **completed** a **clinical trial** that studied an investigational product (drug, biological product, ... How do I indicate that results **need not** be **submitted** for this trial? .... errors, deficiencies, or inconsistencies that are **not** detected automatically during data **entry**. ... Yes, you can register a study on ClinicalTrials.gov at any **time**.
Final Rule for Clinical Trials ... · Applicable Clinical Trial

ClinicalTrials.gov: Requirements and Implementation Strategies
https://prsinfo.clinicaltrials.gov/.../Wong-Williams-RAPS-Regulatory-Focus-8May201...
Since its launch, the policies and **laws** related to registration of **clinical trials** ... is **completed**, the results must be **submitted** to ClinicalTrials.gov via the PRS **no** ... The report is available in the PRS for organizations and individuals in real **time** and may ... Lessons learned have shown basic results **entries** have fewer errors and ...

People also ask

What does NCT stand for in clinical trials?

What is the Fdaaa?

What is a registrational clinical trial?

What is the NCT number?

Feedback

[PDF] ClinicalTrials.gov Protocol Review Criteria - ClinicalTrials.gov Final ...
https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf
5 days ago - for **Clinical Trials** Registration and Results Information **Submission** (42 CFR Part 11). ... Outcome Measure Titles do **not** end with a **period**. ... The **entries** for each data element are consistent with the Protocol Registration Data ... Acronyms used to identify the study are **provided** in the Acronym data element.

Why Should I Register and Submit Results? - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/background
An **entry** on ClinicalTrials.gov that contains a summary of a **clinical study's** ... Why Do I **Need** to Register My Trial and **Submit** Results to ClinicalTrials.gov? ... Study is an Applicable **Clinical Trial** (PDF) (June 2018) for **complete** statutory ... A summary of key **laws** and policies requiring **clinical trial** registration is **provided** in the ...

History, Policies, and Laws - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/about-site/history
The first U.S. Federal **law** to require trial registration was the Food and Drug ... At the **time**, ClinicalTrials.gov primarily included NIH-funded studies. ... In 2007 the **requirements** for **submission** to ClinicalTrials.gov were expanded after Congress .... of whether the **clinical trial** was **completed** as planned or terminated earlier.

About the Results Database - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/about-site/results
Results information for registered and **completed studies** is **submitted** by the **study** ... The "basic" results information **required** by FDAAA 801 includes the following: ... started, **completed**, and dropped out of each **period** of the **study** based on the ... The **study** may **not** be subject to U.S. Federal **requirements** to **submit** results.

[PDF] Changes from Current Practice Described in the Final Rule: Final Rule ...
https://prsinfo.clinicaltrials.gov/FinalRuleChanges-12Dec2016.pdf
Dec 1, 2016 - For a **complete** discussion of the **requirements** and ... Results information is **required** for ALL applicable **clinical trials** that ... deadline for results information **submission** is **no** later than one year ... 3 provides a summary of the data elements with shorter update **times**. .... only if the **entry** for U.S. Food and Drug.

How to Register Your Study - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/how-register
Some data elements are **required** by ClinicalTrials.gov, while others are optional ... to **submit** all data elements in order to provide a **complete** description of the **study**. ... Observational **Study** Model, **Time** Perspective, and Biospecimen information. ... possible), meaningful **entries**, logic and internal consistency, and formatting.

PRS User's Guide - ClinicalTrials.gov Final Rule Information
https://prsinfo.clinicaltrials.gov/prs-users-guide.html
Mar 22, 2018 - U.S. **law** requires some studies to **submit** results to ClinicalTrials.gov. ... Rule for **Clinical Trials** Registration and Results Information **Submission** (42 CFR Part 11). ... **Entry Completed**, User has **finished** and clicked on **Entry Complete**. ..... Optional fields are **not required** for posting on ClinicalTrials.gov, but ...

Searches related to site:clinicaltrials.gov The entry for this clinical trial was not complete at the time of submission, as required by law.

applicable clinical trial **checklist**

clinical **trials registration and results information** submission

42 cfr part 11

trial **reporting in clinicaltrials.gov -** the **final rule**

requirements for clinical **trials**

what is a registration clinical trial

clinicaltrials.gov organization

unique protocol identification number

EXHIBIT I

Google site:clinicaltrials.gov “The entry for this clinical trial was found to be false

All News Videos Images Shopping More Settings Tools

2 results (0.62 seconds)

No results found for **site:clinicaltrials.gov “The entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law.”**.

Results for **site:clinicaltrials.gov The entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law.** (without quotes):

[PDF] A comparative, controlled, clinical investigation of a ... - ClinicalTrials.g...
https://clinicaltrials.gov/ProvidedDocs/74/NCT03498274/Prot_001.pdf
Dec 21, 2017 - **Study** Type: **Clinical** Investigation with Medical Device (MD). **Study** Categorisation: Category C: Medical Device without CE mark. **Study** Registration: SNCTP ... information may **not** - in full or in part - be transmitted, reproduced, published, or disclosed to others ..... **Compliance** with **study** intervention .

[PDF] research protocol - ClinicalTrials.gov
https://clinicaltrials.gov/ProvidedDocs/91/NCT03435991/Prot_SAP_000.pdf
Aug 11, 2017 - European Union. EudraCT. European drug regulatory affairs **Clinical Trials**. GCP .... patient **compliance**: only 11% actual **compliance**, but up to 80% **fake compliance** was determined, the latter presumably .... **Therefore**, we do **not** expect to find perfect correlation coefficients, i.e. >0.8. Correlation coefficients ...

EXHIBIT J

Google site:clinicaltrials.gov "The entry for this clinical trial did not contain inform

All News Videos Images Shopping More Settings Tools

About 74,400 results (0.91 seconds)

No results found for **site:clinicaltrials.gov "The entry for this clinical trial did not contain information on the primary and secondary outcomes at the time of submission, as required by law."**.

Results for **site:clinicaltrials.gov The entry for this clinical trial did not contain information on the primary and secondary outcomes at the time of submission, as required by law.** (without quotes):

Frequently Asked Questions - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/faq
Am I **required** to **submit** results **information** for my applicable **clinical trial** (ACT)?; When is **required clinical trial** results **information** due? ... to ClinicalTrials.gov, that **information** undergoes a manual review to identify possible errors, deficiencies, or inconsistencies that **are not** detected automatically during data **entry**.
Final Rule for Clinical Trials ... · Applicable Clinical Trial · Registration Information ...

About the Results Database - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/about-site/results
The **submission** of adverse event **information was** optional when the results database **was** first released but **was required** beginning in September 2009. ... It includes tables for each prespecified **Primary** Outcome and **Secondary Outcome** and may also include other prespecified outcomes, post hoc outcomes, and any ...

FDAAA 801 and the Final Rule - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/fdaaa
The Final Rule for **Clinical Trials** Registration and Results **Information Submission** (42 CFR Part 11), which clarifies and expands the **requirements** in FDAAA 801 ... a **clinical trial** to test prototype devices, where the **primary outcome** measure relates to feasibility and not to health **outcomes** (see note); Trials that **do not** include ...
Who Is Responsible for ... · Which Trials Must Be ... · When Do I Need to Register ...

PRS User's Guide - ClinicalTrials.gov Final Rule Information
https://prsinfo.clinicaltrials.gov/prs-users-guide.html
Mar 22, 2018 - Anyone who enters **clinical study information** into the Protocol Registration and Results System (PRS) must **have** an account. ..... including each **primary** and **secondary outcome** measure, must generally be **submitted** within 1 year of the **Primary** Completion Date for applicable **clinical trials required** to be ...

ClinicalTrials.gov Protocol Registration Data Element Definitions for ...
https://prsinfo.clinicaltrials.gov/definitions.html
Jun 29, 2017 - This document describes the definitions for protocol registration data elements **submitted** to ClinicalTrials.gov for interventional studies (**clinical trials**) and ... Data element **entries are** annotated with symbols to indicate generally what **information is required** to be **submitted** (and under which circumstances).

How to Submit Your Results - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/how-report
For certain **clinical trials** subject to the **requirements** of Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), Responsible Parties must **submit** ... Summary results **information** may be **submitted** once data **are** available for one or more **primary outcome** measures and for each arm of the study.

ClinicalTrials.gov Results Data Element Definitions for Interventional ...
https://prsinfo.clinicaltrials.gov/results_definitions.html
Mar 22, 2018 - This document describes the definitions for results data elements **submitted** to ClinicalTrials.gov for interventional studies (**clinical trials**) and .... A table of data for each **primary** and **secondary outcome** measure by arm (that **is**, initial assignment of participants to arms or groups) or comparison group (that **is**, ...

[PDF] Overview of Ove v ew o ClinicalTrials.gov Outline
https://prsinfo.clinicaltrials.gov/webinars/module1/resources/Overview_Handouts.pdf
Results **Information**. • Participant Flow. • Baseline and Demographic Characteristics. g p. • **Primary** and **Secondary Outcomes**. • Adverse Event **information** ... Interventional **trials**. D bi l i d i. • Drugs, biologics, devices. – **Not** phase 1 **drug** or **not** small feasibility device. – US FDA jurisdiction (e.g., IND/IDE or U.S. site). 17.

[PDF] Submitting Results Data: Outcome Measures and Statistical Analyses ...
https://prsinfo.clinicaltrials.gov/webinars/module7/.../OutcomeMeasures_Transcript.pd...
analyses for each pre-specified **primary** and **secondary outcome** measure. Other outcome measures may also be included in this module. The **law** requires ... Here **is** one from a journal article that shows the three arms of the **clinical trial** and the ... In the future, we intend to **have** this as a data **entry** mode as sort of a wizard.

Learn About Clinical Studies - ClinicalTrials.gov
https://clinicaltrials.gov/ct2/about-studies/learn
Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that **contains** no active ingredients, or to no intervention. Some **clinical trials** compare interventions that are already available to each other. When a new product or approach is being studied, it **is not** usually known ...

Searches related to site:clinicaltrials.gov The entry for this clinical trial did not contain information on the primary and secondary outcomes at the time of submission, as required by law.

clinical trials registration and results information submission

fdaaa 801

42 cfr part 11

trial reporting in clinicaltrials.gov - the final rule

applicable clinical trial checklist

clinical trials gov api

clinical trial results database

fda gov clinical trials

EXHIBIT K

Advanced Search

Fill in any or all of the fields below. Click on the label to the left of each search field for more information or read the Help

Search Help

Condition or disease:

Other terms:

Study type:
All Studies

Study Results:
All Studies

Recruitment status:

Clinical study:

- [ ] Not yet recruiting
- [ ] Recruiting
- [ ] Enrolling by invitation
- [ ] Active, not recruiting
- [ ] Suspended
- [ ] Terminated
- [ ] Completed
- [ ] Withdrawn
- [ ] Unknown status

Expanded Access:

- [ ] Available

- [ ] No longer available
- [ ] Temporarily not available
- [ ] Approved for marketing

Eligibility Criteria:

Age:

[ ] x years OR **Age Group:**

- [ ] Child (birth–17)
- [ ] Adult (18–65)
- [ ] Senior (66+)

Sex:

All x

Accepts Healthy Volunteers:

- [ ] Healthy volunteers may participate in the study

Targeted Search:

Intervention/treatment:

x

Title / Acronym:

x

Outcome Measure:

x

Sponsor / Collaborator:

x

- [ ] Exact match

Sponsor (Lead):

x

- [ ] Exact match

Study IDs:

x

Locations:

Country:

Location Terms:

Additional Criteria:

Phase:

- [ ] Early Phase 1
- [ ] Phase 1
- [ ] Phase 2
- [ ] Phase 3
- [ ] Phase 4

Funder Type:

- [ ] NIH
- [ ] Other U.S. Federal agency
- [ ] Industry
- [ ] All others (individuals, universities, organizations)

Study Start:

From

To

(MM/DD/YYYY)

Primary Completion:

From

To

(MM/DD/YYYY)

First Posted:

From

To

(MM/DD/YYYY)

Last Update Posted:

From

To

(MM/DD/YYYY)

Search Help

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